REMARKS

Request for Substitution of Sequence Listing based upon Deposit

At the outset, Applicants respectfully request substitution of the sequence listing on file with the sequence listing submitted herewith. Upon resequencing the plasmid, 18GC, identified in the instant application (SEQ ID NOS:3 and 4), Applicants noted five nucleotide discrepancies resulting in one amino acid change in the sequences. Applicants have deposited the plasmid identified in the application with the ATCC on September 10, 2002. The deposit has been accepted and designated PTA-4654. Applicants, in the instant Response, seek to incorporate the correct sequence into the application with deposit, the substitute sequence listing based upon the deposit, amended specification, amended drawings, and declaration. Examination of the proper sequences is respectfully requested.

Status of the Claims

Claims 1-92 are currently pending. Claims 1-23, 36-63, 65-85, and 88-92 were withdrawn from further consideration in response to a restriction requirement by the Examiner, under 37 C.F.R. §1.142(b).

In the present Response, claims 24-35, 64, 86, and 87 are cancelled, without prejudice; and new claims 93-119 are added. Thus, after entry of these amendments, claims 93-119 are presented for consideration.

Outstanding Rejections

Pursuant to the Office Action, claims 24-35, 64, and 86-87 are rejected under 35 U.S.C. §112, second paragraph. Claims 24-35 and 86-87 are rejected under 35 U.S.C. §112, first paragraph. Claims 24-35 and 64 are rejected under 35 U.S.C. §102 as allegedly anticipated by Kawarabayasi *et al.* PIR accession number E71144, August 14, 1998, (hereinafter "Kawarabayasi"). Claims 86-87 are rejected under 35 U.S.C. § 103(a) for allegedly being unpatentable over Kawarabayasi. Claims 24-35, 64, and 86-87 are rejected under the judicially

created doctrine of obviousness-type double patenting for allegedly being unpatentable over claims 1 and 15 of U.S. Patent No. 5,958,751. Claims 24-35, 64, and 86-87 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 10 and 11 of copending Application No. 09/407,806. Applicants respectfully traverse all outstanding objections to the specification and rejection of the claims.

Support for the Claim Amendments

Support for the new claims can be found throughout the specification, in particular, the claims 1, 17, 22-35, 64, 86, and 87, as originally filed. Claims directed to a purified polypeptide having at least 10, 15, 20, 25, 30, 35, 40, 45, 75, 100, and 150 amino acids of the claimed polypeptide and having α-galactosidase activity can be found, *inter alia,* at page 51, lines 1-6. Claims 116 and 117 are supported at least by originally filed claim 64. Claims 118 and 119 are supported at least by originally filed claims 86 and 87. Accordingly, Applicants submit that no new matter is introduced by the instant amendments.

Objections to the Specification

The Patent Office notes the use of trademarks in the application, pointing to "STRATEGENE," and "BECKMAN," etc. in pages 71-72.[1] Applicants submit that the use of the terms "STRATEGENE" and "BECKMAN" on pages 71-72 is as company names and not as trademarks. The specification has been amended to acknowledge trademarks used in the specification.

The Patent Office alleges that the title of the invention is not descriptive. The Patent Office has suggested the title "*Thermococcus alcaliphilus* enzymes having α-galactosidase activity and methods of use thereof."[2] Applicants respectfully submit that such a title would be less descriptive of the claimed invention. An enzyme from *Thermococcus alcaliphilus* having α-galactosidase activity is but one exemplary enzyme of the invention. Accordingly, Applicants have amended the claim to "α-galactosidases and methods for making and using them."

---

[1] See page 3, lines 2-4, of the Office Action.
[2] See page 3, lines 8-11, of the Office Action.

Objections to the Drawings

The drawings are objected to under 37 I.E. §1.84 or 1.152 by the Draftsperson. Applicants herewith submit a set of formal drawings to overcome the objections raised by the Draftsperson. In addition, Applicants respectfully request entry of the amendment to the drawings shown in red. Corrections to the sequence are being submitted upon the result of the resequenced plasmid, 18GC. The plasmid has been deposited with the ATCC on September 10, 2002. No new matter is added by the formal drawings.

Objections to the Claims

Claims 24-35, 64, and 86-87 are objected to for depending on non-elected claims. Applicants have cancelled these claims, thereby rendering this objection moot.

Issues under 35 U.S.C. §112, second paragraph

Claims 24-35, 64, and 86-87 are rejected under 35 U.S.C. §112, second paragraph, for allegedly being indefinite. Namely, claims 24 and 35 are alleged to be indefinite in the recitation of "substantially identical." Claims 24-35, 64, and 86-87 are alleged to be indefinite in the recitation of "polypeptide of claims 22 or 23," "polypeptide of claims 17 or 25," or "polypeptide of claim 1." Claims 25-34 are alleged to be indefinite in the recitation of "#% homology." Claims 25-28, 30, 32-34 (claims 86-87 dependent thereon) are alleged to be indefinite in the recitation of "at least about." Claim 35 is alleged to be indefinite in the recitation of "polypeptide having a sequence as set forth in SEQ ID NO:4 and sequences substantially identical thereto." Claim 64 is alleged to be indefinite in the recitation of "which is stable to heat, is heat resistant and ....temperatures of from about 60 degrees to ..."[3] Applicants have cancelled claims 24-35, 64, and 86-87, thereby rending these rejections moot. Applicants submit that these rejections are not applicable to the newly added claims.

[3] See page 4, line 16, to page 6, line 11, of the Office Action.

Issues under 35 U.S.C. §112, second paragraph

Claims 24-35 and 86-87 are rejected under 35 U.S.C. § 112, first paragraph, for allegedly containing subject material not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The Patent Office alleges that claims 24-34 and 86-87 are directed to genera of polypeptides of any function wherein the polypeptide (1) comprise at least 10 consecutive amino acids of the polypeptide of SEQ ID NO:4 or (2) have an amino acid sequence which is at least 50%-95% identical to that of SEQ ID NO:4 or a polypeptide comprising 10 consecutive amino acids of SEQ ID NO:4.

Applicants have cancelled claims 24-34 and 86-87, thereby rendering this rejection moot. Applicants submit that this rejection is not applicable to the newly added claims. For example, new claims 93-116 are directed to polypeptides having α-galactosidase activity. Thus, the new claims are not directed to a genera of polypeptides of any function.

Applicants submit that the instant application sufficiently describes the claimed invention to the skilled artisan. The skilled artisan is well versed in protocols used in the laboratory for biological research. The instant application provides the amino acid sequence, provides the information in assessing percent homologies, and an assay to test the polypeptide for its activity. Armed with this information and drawing upon his or her knowledge and experience in the field, the skilled artisan would have found the claimed invention to be adequately described in the application.

The Patent Office further alleges that the specification is silent with regard to the enzyme's stability to heat and its ability to renature and regain activity after exposure to temperatures of 60 to 105 degrees C.[4] Applicants respectfully submit that the skilled artisan would be able to assess whether the enzyme has the ability to renature and regain activity after

[4] See page 7, lines 15-17, of the Office Action.

exposure to temperatures of about 60 degrees to 105 degrees since the specification provides an exemplary assay for testing the activity of the enzyme.

The Patent Office alleges that the state of the art teaches that sequence comparison alone should not be used to determine a protein's function and that small amino acid changes can drastically change the function of a polypeptide, looking to three references, Bork, Van de Loo, and Broun. Thus, the Patent Office maintains that many functionally unrelated polypeptides are encompassed within the scope of these claims.[5] Applicants respectfully submit that the new claims are limited to polypeptides having α-galactosidase activity; therefore, functionally unrelated polypeptides would not be encompassed by the scope of these claims. Accordingly, Applicants respectfully submit the claims are sufficiently described in the instant specification.

Claims 24-35, 64, and 86-87 are rejected under 35 U.S.C. §112, first paragraph, for allegedly not being enabled by the instant specification. While the Patent Office acknowledges that the polypeptide of SEQ ID NO:4 or the polypeptide encoded by the polynucleotide of SEQ ID NO:3 is enabled, it does not agree that polypeptides which comprise at least 10 consecutive amino acids of the polypeptide of SEQ ID NO:4, (2) which have an amino acid sequence which is at least 50%-95% identical to that of SEQ ID NO:4, or any polypeptide comprising 10 consecutive amino acids of SEQ ID NO:4, or (3) having α-galactosidase activity which are encoded by a nucleic acid comprising a nucleotide sequence of at least 50% sequence identity to SEQ ID NO:3 wherein the polypeptide is stable to heat, catalyses the hydrolysis of saccharides, and is able to regain activity after exposure to temperatures of 60 to 105 degrees, are enabled.[6]

Applicants respectfully disagree; however, claims 24-35, 64, and 86-87 have been cancelled and the rejection has been rendered moot as to these claims. To the extent that the Patent Office wishes to apply this rejection to the added claims, Applicants respectfully submit that the new claims are enabled by the specification.

---

[5] See page 7, line 18, to page 8, line 7, of the Office Action.
[6] See page 8, lines 12-21, of the Office Action.

The Patent Office alleges that there is no disclosure of the function of the polypeptides encompassed by the claims, nor any information as to which structural elements are related to α-galactosidase activity, and the specification is silent to the enzyme's stability to heat or renature and regain activity after exposure to 60 to 105 degrees C. Thus, the Patent Office alleges that to practice the invention would require undue experimentation.[7]

In the instant application, Applicants have disclosed the amino acid sequence (*i.e.*, structure) of a novel polypeptide having α-galactosidase activity. It should be mentioned that at the time the instant application was filed, the state of the art and level of skill of the artisan in the field of molecular biology was very advanced. For example, thermostable \Ther'mo*sta"ble\, a. [Thermo- + stable fixed.] (Physiol. Chem.) is defined as the "capable of being heated to or somewhat above 55[deg] C. without loss of special properties; -- said of immune substances, etc." Webster's Revised Unabridged Dictionary, © 1996, 1998 MICRA, Inc, Thus, armed with the disclosure provided in the application, one of ordinary skill in the art can use well-known properties and well-known laboratory techniques to create variant thermostable polypeptides having at least 70% identity and also polypeptides having at least 10 consecutive amino acids of SEQ ID NO:4 or its variants. The disclosure provides an exemplary assay for testing the polypeptides for activity (see page 71 of the specification).

Accordingly, based on Applicants' disclosure, the claimed invention is properly enabled for one skilled in the art to practice the invention. The Patent Office has alleged that this is undue experimentation. Applicants respectfully aver, however, that it would be a matter of routine experimentation, not undue experimentation, for one skilled in the art.

Regarding undue experimentation, the Federal Circuit in *In re Wands* directed that the focus of the enablement inquiry should be whether the experimentation needed to practice the invention is or is not "undue" experimentation. The court set forth specific factors to be considered.

---

[7] See page 9, lines 3-18, of the Office Action.

One of these factors is "the quantity of experimentation necessary." Guidance as to how much experimentation may be needed and still not be "undue" is set forth by the Federal Circuit in, *e.g.*, *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*[8] An applicant had claims that were generic to all IgM antibodies directed to a specific antigen. However, only a single antibody producing cell line had been deposited.[9] The PTO had rejected claims that were generic to all antibodies directed to the antigen as lacking an enabling disclosure.

The Federal Circuit reversed, noting that the evidence indicated that those skilled in the monoclonal antibody art could, using the state of the art and applicants' written disclosure, produce and screen new hybridomas secreting other monoclonal antibodies falling within the genus without undue experimentation. The court held that applicants' claims need not be limited to the specific, single antibody secreted by the deposited hybridoma cell line (significantly, the genus of antibodies was allowed even though only one antibody species was disclosed). The court was acknowledging that, because practitioners in that art are prepared to screen large numbers of negatives in order to find a sample that has the desired properties, the screening that would be necessary to make additional antibody species was not "undue experimentation."

Analogously, practitioners of molecular biology for the instant invention also recognize that many constructs may need to be created/isolated and analyzed to isolate the claimed polypeptides and polynucleotides. However, the procedures for isolating the polypeptides, creating variant polypeptides, and utilizing the sequences provided, for such things as the construction of probes, are widely accepted, routine protocols not requiring "undue experimentation" to be practiced. Accordingly, the skilled artisan has sufficient guidance from the specification to practice the claimed methods without undue experimentation.

In light of the amendments and arguments presented herein, Applicants respectfully submit that the rejection based upon 35 U.S.C. §112, first paragraph, is not applicable to the added claims.

---

[8] *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987).

[9] The cell line was a hybridoma, thus, all of the antibodies it produced had the same structure and activity.

Issues under 35 U.S.C. §§102 and 103

Claims 24-35 and 64 are rejected under 35 U.S.C. §102(b) as allegedly anticipated by Kawarabayasi. Claims 86 and 87 are rejected under 35 U.S.C. §103(a) for allegedly being unpatentable over Kawarabayasi. To the extent that these rejections are applied to the new claims, Applicants respectfully submit that Kawarabayasi is not a proper prior art reference.

It is stated that the Kawarabayasi sequence became available to the public on August 14, 1998. However, Applicants respectfully submit that the instant application is entitled to claim priority all the back to at least March 8, 1996, the filing date of U.S. Patent Application Serial No. 08/613,220, in which the plasmid 18GC is identified. Applicants herewith submit an amended sequence listing (paper copy and computer readable form) from the re-sequence clone 18GC, submitted to the ATCC on September 10, 2002.

Therefore, because the priority date of the instant invention, March 8, 1996, predates Kawarabayasi's date of publication August 14, 1998, Kawarabayasi is not a proper prior art reference. As such, Applicants respectfully submit Kawarabayasi does not anticipate nor render obvious the claimed invention.

Issues regarding Double Patenting

Claims 24-35, 64, and 86-87 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 15 of U.S. Patent No. 5,958,751. To the extent that this rejection applies to claims 93-119, Applicants have submitted a terminal disclaimer to overcome this rejection.

Claims 24-35, 64, and 86-87 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 10 and 11 of copending application serial no. 09/407,806. As the Patent Office has noted, this is a provisional rejection because the conflicting claims have not in fact been patented. Applicants will hold this issue in abeyance until such time the claims are held allowable.

CONCLUSION

Claims 24-35, 64, and 86-87 are pending in the application. Claims 1-92 have been cancelled, without prejudice; and claims 93-119 have been added by the instant Response. Applicants request that the Examiner reconsider the application and claims in light of the foregoing reasons and amendments and respectfully submit that the claims are in condition for allowance.

If, in the Examiner's opinion, a telephonic interview would expedite the favorable prosecution of the present application, the undersigned attorney would welcome the opportunity to discuss any outstanding issues and to work with the Examiner toward placing the application in condition for allowance.

Attached is a marked-up version of the changes being made by the current amendment.

Applicants believe that no additional fees are necessitated by the instant Response. However, in the event any fees are due, the Commissioner is hereby authorized to charge any such fees to Deposit Account No. 06-1050.

Respectfully submitted,

Date: 12/18/2002

Mi K. Kim
Reg. No. 44,830

Fish & Richardson P.C.
4350 La Jolla Village Drive, Suite 500
San Diego, California 92122
Telephone: (858) 678-5070
Facsimile: (858) 678-5099

Version with markings to show changes made

In the specification:

The title has been amended as follows:

ALPHA GALACTOSIDASES AND METHODS FOR MAKING AND USING THEM [ENZYMES HAVING ALPHA-GALACTOSIDASE ACTIVITY AND METHODS OF USE THEREOF]

Paragraph beginning at page 24, line 24, has been amended as follows:

As representative examples of expression vectors which may be used, there may be mentioned viral particles, baculovirus, phage, plasmids, phagemids, cosmids, fosmids, bacterial artificial chromosomes, viral DNA (*e.g.*, vaccinia, adenovirus, foul pox virus, pseudorabies and derivatives of SV40), P1-based artificial chromosomes, yeast plasmids, yeast artificial chromosomes, and any other vectors specific for specific hosts of interest (such as bacillus, aspergillus and yeast). Thus, for example, the DNA may be included in any one of a variety of expression vectors for expressing a polypeptide. Such vectors include chromosomal, nonchromosomal and synthetic DNA sequences. Large numbers of suitable vectors are known to those of skill in the art, and are commercially available. The following vectors are provided by way of example; Bacterial: pQE vectors (Qiagen), pBLUESCRIPT® [pBluescript] plasmids, pNH vectors, (lambda-ZAP vectors (Stratagene); ptrc99a, pKK223-3, pDR540, pRIT2T (Pharmacia); Eukaryotic: pXT1, pSG5 (Stratagene), pSVK3, pBPV, pMSG, pSVLSV40 (Pharmacia). However, any other plasmid or other vector may be used so long as they are replicable and viable in the host. Low copy number or high copy number vectors may be employed with the present invention.

Paragraph beginning at page 43, line 30, has been amended as follows:

Particular bacterial vectors which may be used include the commercially available plasmids comprising genetic elements of the well known cloning vector pBR322 (ATCC 37017), pKK223-3 (Pharmacia Fine Chemicals, Uppsala, Sweden), GEM1 (Promega Biotec, Madison,

Wis., USA) pQE70, pQE60, pQE-9 (Qiagen), pD10, psiX174 pBLUESCRIPT® [pBluescript] II KS, pNH8A, pNH16a, pNH18A, pNH46A (Stratagene), ptrc99a, pKK223-3, pKK233-3, pDR540, pRIT5 (Pharmacia), pKK232-8 and pCM7. Particular eukaryotic vectors include pSV2CAT, pOG44, pXT1, pSG (Stratagene) pSVK3, pBPV, pMSG, and pSVL (Pharmacia). However, any other vector may be used as long as it is replicable and viable in the host cell.

Paragraph beginning at page 58, line 29, has been amended as follows:

A "comparison window", as used herein, includes reference to a segment of any one of the number of contiguous positions selected from the group consisting of from 20 to 600, usually about 50 to about 200, more usually about 100 to about 150 in which a sequence may be compared to a reference sequence of the same number of contiguous positions after the two sequences are optimally aligned. Methods of alignment of sequence for comparison are well-known in the art. Optimal alignment of sequences for comparison can be conducted, *e.g.*, by the local homology algorithm of Smith & Waterman, Adv. Appl. Math. 2:482, 1981, by the homology alignment algorithm of Needleman & Wunsch, J. Mol. Biol 48:443, 1970, by the search for similarity method of person & Lipman, Proc. Nat'l. Acad. Sci. USA 85:2444, 1988, by computerized implementations of these algorithms (GAP, BESTFIT, FASTA, and TFASTA in the Wisconsin Genetics Software Package, Genetics Computer Group, 575 Science Dr., Madison, WI), or by manual alignment and visual inspection. Other algorithms for determining homology or identity include, for example, in addition to a BLAST™ program (Basic Local Alignment Search Tool at the National Center for Biological Information), ALIGN, AMAS™ (Analysis of Multiply Aligned Sequences), AMPS™ (Protein Multiple Sequence Alignment), ASSET™ (Aligned Segment Statistical Evaluation Tool), BANDS, BESTSCOR, BIOSCAN™ (Biological Sequence Comparative Analysis Node), BLIMPS (BLocks IMProved Searcher), FASTA, Intervals & Points, BMB, CLUSTAL V, CLUSTAL W, CONSENSUS™, LCONSENSUS, WCONSENSUS, Smith-Waterman algorithm, DARWIN™, Las Vegas algorithm, FNAT (Forced Nucleotide Alignment Tool), Framealign, [Framesearch] FRAMESEARCH™, DYNAMIC™, FILTER, FSAP (Fristensky Sequence Analysis Package), GAP (Global Alignment Program), GENAL, GIBBS™, [GenQuest] GENQUEST™, ISSC™ (Sensitive Sequence Comparison), LALIGN (Local Sequence Alignment), LCP™ (Local Content Program), MACAW™ (Multiple Alignment

Construction & Analysis Workbench), MAP (Multiple Alignment Program), MBLKP, MBLKN, PIMA (Pattern-Induced Multi-sequence Alignment), SAGA™ (Sequence Alignment by Genetic Algorithm) and WHAT-IF. Such alignment programs can also be used to screen genome databases to identify polynucleotide sequences having substantially identical sequences. A number of genome databases are available, for example, a substantial portion of the human genome is available as part of the Human Genome Sequencing Project (J. Roach[, http://weber.u.Washington.edu/~roach/human_ genome_ progress 2.html]) (Gibbs, 1995). At least twenty-one other genomes have already been sequenced, including, for example, *M. genitalium* (Fraser *et al.*, 1995), M. jannaschii (Bult *et al.*, 1996), *H. influenzae* (Fleischmann *et al.*, 1995), *E. coli* (Blattner *et al.*, 1997), and yeast (*S. cerevisiae*) (Mewes *et al.*, 1997), and *D. melanogaster* (Adams *et al.*, 2000). Significant progress has also been made in sequencing the genomes of model organism, such as mouse, *C. elegans*, and *Arabadopsis sp.* Several databases containing genomic information annotated with some functional information are maintained by different organization, and are accessible via the internet, for example, the website for The Institute For Genomic Research [http://wwwtigr.org/tdb]; the genetics website for the University of Wisconsin - Madison [http://www.genetics.wisc.edu]; the Stanford University Genomic Resources website [http://genome-www.stanford.edu/~ball]; the website for the HIV database [http://hiv-web.lanl.gov]; the website for the National Center for Biotechnology Information [http://www.ncbi.nlm.nih.gov]; the website for the European Bioinformatics Institute [http://www.ebi.ac.uk]; the website for the Institut Pasteur [http://Pasteur.fr/other/biology]; and the website for the Whitehead Institute/MIT Center for Genome Research [http://www.genomc.wi.mit.edu].

Paragraph beginning at page 60, line 7, has been amended as follows:

One example of a useful algorithm is BLAST and BLAST 2.0 algorithms, which are described in Altschul *et al.*, Nuc. Acids Res. 25:3389-3402, 1977, and Altschul *et al.*, J. Mol. Biol. 215:403-410, 1990, respectively. Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information website [(http://www.ncbi.nlm.nih.gov/)]. This algorithm involves first identifying high scoring sequence

pairs (HSPs) by identifying short words of length W in the query sequence, which either match or satisfy some positive-valued threshold score T when aligned with a word of the same length in a database sequence. T is referred to as the neighborhood word score threshold (Altschul *et al.*, *supra*). These initial neighborhood word hits act as seeds for initiating searches to find longer HSPs containing them. The word hits are extended in both directions along each sequence for as far as the cumulative alignment score can be increased. Cumulative scores are calculated using, for nucleotide sequences, the parameters M (reward score for a pair of matching residues; always >0). For amino acid sequences, a scoring matrix is used to calculate the cumulative score. Extension of the word hits in each direction are halted when: the cumulative alignment score falls off by the quantity X from its maximum achieved value; the cumulative score goes to zero or below, due to the accumulation of one or more negative-scoring residue alignments; or the end of either sequence is reached. The BLAST algorithm parameters W, T, and X determine the sensitivity and speed of the alignment. The BLASTN program (for nucleotide sequences) uses as defaults a wordlength (W) of 11, an expectation (E) of 10, M=5, N=-4 and a comparison of both strands. For amino acid sequences, the BLASTP program uses as defaults a wordlength of 3, and expectations (E) of 10, and the BLOSUM62 scoring matrix (see Henikoff & Henikoff, Proc. Natl. Acad. Sci. USA 89:10915, 1989) alignments (B) of 50, expectation (E) of 10, M=5, N= -4, and a comparison of both strands.

Paragraph beginning at page 61, line 21, has been amended as follows:

The BLAST programs identify homologous sequences by identifying similar segments, which are referred to herein as "high-scoring segment pairs," between a query amino or nucleic acid sequence and a test sequence which is preferably obtained from a protein or nucleic acid sequence database. High-scoring segment pairs are preferably identified (*i.e.*, aligned) by means of a scoring matrix, many of which are known in the art. Preferably, the scoring matrix used is the BLOSUM62 matrix (Gonnet *et al*, Science 256:1443-1445, 1992; Henikoff and Henikoff, Proteins 17:49-61, 1993). Less preferably, the PAM or PAM250 matrices may also be used (see, *e.g.*, Schwartz and Dayhoff, eds., 1978, *Matrices for Detecting Distance Relationships: Atlas of Protein Sequence and Structure*, Washington: National Biomedical Research Foundation). BLAST programs are accessible through the U.S. National Library of Medicine, *e.g.*, at the website for the National Center for Biotechnology Information [www.ncbi.nlm.nih.gov].

Paragraph beginning at page 66, line 19, has been amended as follows:

Figure 5 is a flow diagram illustrating one embodiment of an identifier process 300 for detecting the presence of a feature in a sequence. The process 300 begins at a start state 302 and then moves to a state 304 wherein a first sequence that is to be checked for features is stored to a memory 115 in the computer system 100. The process 300 then moves to a state 306 wherein a database of sequence features is opened. Such a database would include a list of each feature's attributes along with the name of the feature. For example, a feature name could be "Initiation Codon" and the attribute would be "ATG". Another example would be the feature name "TAATAA Box" and the feature attribute would be "TAATAA". An example of such a database is produced by the University of Wisconsin Genetics Computer Group [(www.gcg.com)]. Alternatively, the features may be structural polypeptide motifs such as alpha helices, beta sheets, or functional polypeptide motifs such as enzymatic active sites, helix-turn-helix motifs or other motifs known to those skilled in the art.

Paragraph beginning at page 71, line 6, has been amended as follows:

Colonies containing pBLUESCRIPT® [pBluescript] plasmids with random inserts from the organism *Thermococcus alcaliphilus* AEDII12RA were obtained from an original XZAP2 genomic library generated according to the manufacturer's (Stratagene) protocol. The clones were then excised from λZAP2 to pBLUESCRIPT® [pBluescript]. The clones were excised to pBLUESCRIPT® [pBluescript] according to the method of Hay and Short. (Hay, B. and Short, J. Strategies, 1992, 5:16.) The resulting colonies were picked with sterile toothpicks and used to singly inoculate each of the wells of 96-well microtiter plates. The wells contained 250 μL of LB media with 100 μg/ml methicillin, and 10% v/v glycerol (LB Amp/Meth, glycerol). The cells were grown overnight at 37°C. without shaking. This constituted generation of the "Source GeneBank"; each well of the Source GeneBank thus contained a stock culture of *E. coli* cells, each of which contained a pBLUESCRIPT® [pBluescript] plasmid with a unique DNA insert.

Paragraph beginning at page 71, line 21, has been amended as follows:

The plates of the Source GeneBank were used to multiply inoculate a single plate (the "Condensed Plate") containing in each well 200 µL of LB Amp/Meth, glycerol. This step was performed using the High Density Replicating Tool (HDRT) of the Beckman BIOMEK® [Biomek] with a 1% bleach, water, isopropanol, air-dry sterilization cycle in between each inoculation. Each well of the Condensed Plate thus contained 10 to 12 different pBLUESCRIPT® [pBluescript] clones from each of the source library plates. The Condensed Plate was grown for 16 h at 37° C. and then used to inoculate two white 96-well Polyfiltronics microtiter daughter plates containing in each well 250 µL of LB Amp/Meth (without glycerol). The original condensed plate was put in storage -80° C. The two condensed daughter plates were incubated at 37° C. for 18 h.

In the claims:

Claims 1-92 have been cancelled, without prejudice.